UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/524,787	09/23/2005	Lea Eisenbach	EISENBACH4A	8693

1444 7590 09/01/2009

BROWDY AND NEIMARK, P.L.L.C.
624 NINTH STREET, NW
SUITE 300
WASHINGTON, DC 20001-5303

EXAMINER	
BRISTOL, LYNN ANNE	
ART UNIT	PAPER NUMBER
1643	

MAIL DATE	DELIVERY MODE
09/01/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/524,787	EISENBACH ET AL.	
	Examiner	Art Unit	
	LYNN BRISTOL	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 June 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-7,9,12-17,21-30,36-39,43-46 and 51-64* is/are pending in the application.

4a) Of the above claim(s) *24-29,46,51-58,60 and 61* is/are withdrawn from consideration.

5)☒ Claim(s) *59* is/are allowed.

6)☒ Claim(s) *1, 3-6, 9, 12-17, 21-23, 30, 36-39, 43-45 and 62* is/are rejected.

7)☒ Claim(s) *7,63 and 64* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 6/17/09 has been entered.

2. Claims 1, 3-7, 9, 12-17, 21-30, 36-39, 43-46, and 51-64 are all the pending claims for this application.

3. Claims 32, 33, 35 and 47-50 were cancelled, and Claims 30 and 36-38 were amended in the Response of 6/17/09.

4. Claims 24-29, 46, 51-58, 60 and 61 are withdrawn from examination.

5. Claims 1, 3-7, 9, 12-17, 21-23, 30, 36-39, 43-45, 59 and 62-64 are all the claims under examination.

6. This Office Action contains new grounds for rejection.

Withdrawal of Rejections

Claim Rejections - 35 USC § 112, second paragraph

7. The rejection of Claim 32 under 35 U.S.C. 112, second paragraph, as being indefinite reciting a broadening limitation for the TAA of SEQ ID NO:59 is moot for the cancelled claim.

Claim Rejections - 35 USC § 102

8. The rejection of Claims 30 and 32 under 35 U.S.C. 102(e) as being anticipated by Matsuzaki et al. (US 20030092037; published 5/15/03; filed 7/18/02) is withdrawn.

Applicants have amended Claim 30 to clarify that a 8-10 residue peptide is from the TAA full length sequence of SEQ ID NO: 59 (1-8D) or SEQ ID NO: 61 (????).

9. The rejection of Claim 30 under 35 U.S.C. 102(e) as being anticipated by Berger et al. (US 20030148410; published August 7, 2003; priority to U.S. Provisional Application No. 60/339971, filed December 10, 2001) is withdrawn.

Applicants have amended Claim 30 to clarify that the peptide is capable of promoting effective binding to a MHC class I molecule to elicit a CTL response, and there is no disclosure of such TAA peptides in Berger.

Rejections Maintained

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement (1)

10. The rejection of Claims 15-17, 21-23, 30 and 43-45 (and now Claims 36-39) under 35 U.S.C. 112, first paragraph, is maintained as failing to comply with the

enablement requirement for an intended use for treating or inhibiting the development of colon cancer with the inventive MHC-class I binding, CTL-inducing peptides presented as a "cell composition".

For purposes of review the rejection was maintained in the Office Action of 3/18/08 as follows:

"Applicants' allegations on p. 14 of the Response of 1/10/08 have been considered but are not found persuasive. Applicants allege that in amending the claims to replace the limitation "cellular vaccine composition" with "a cell composition" that the claims are fully enabled (or would otherwise remove the requirement that the composition is a vaccine with intended prophylactic properties).

The examiner submits that in requiring the composition (generic Claims 15 and 30) to comprise a "cell composition" comprising "an antigen presenting cell which presents said at least one peptide", Applicants are required to show with a reasonable number of examples that the peptide(s) in fact could be presented by an APC in order to accomplish the required elicitation of a CTL response. The amendment to delete "vaccine" excludes the requirement that the composition is prophylactic, but the compositions still comprise a literal functional component, the APC, which is a) genetically modified with a polynucleotide encoding the TAA peptide, b) loaded with at least one polynucleotide encoding the TAA peptide, c) loaded with TAA peptides *and/or* d) loaded with polypeptides comprising TAA peptides. The claims embrace recombinant APCs having the ability to express and present the TAA peptide for CTL induction. Applicants' specification does not demonstrate any example of a recombinant APC showing all of the instant claimed characteristics of the compositions. Accordingly, the composition still reads on an intended use where APC is applied in a manner (in vitro or in vivo) to elicit the CTL response that is not fully enabled by the specification at the time of filing."

The rejection was maintained in the Office Action of 12/17/08 as follows:

"Applicants' allegations on pp. 10-11 of the Response of 9/18/08 and the 1.132 Declaration have been considered and are not found persuasive. Applicants allege that a reasonable number of working examples for peptide-loaded APCs under the Wands criteria are demonstrated in Example 1 of the specification and the corresponding Tirosh reference (Brit. J. Can. 97:1655-1663 (2007)). Applicants allege one of ordinary skill in the art would expect that if peptides can be presented by APCs using the loading technique(s) mentioned in the present specification, then one of ordinary skill in the art would also expect that they would also be presented using genetic engineering techniques known in the art.

Response to Arguments

The examiner submits that Applicants wish to obtain patent coverage for any peptide of 8-10 amino acid residues in length from any known or yet to be discovered TAA protein expressed by any human colon carcinoma cells formulated into any antigen presenting cell composition. It is clear from the specification and the Tirosh reference that from *over* 500 putative TAA peptides derived from 26 overexpressed genes in colon carcinoma, that only seven (7) peptides were antigenic and immunogenic in HHD mice. Of these 7, three were from "human 1-8D gene from interferon inducible gene" (peptides 1-6, 3-5 and 3-7), one from actin binding protein (peptide 1-11), one from human ribosomal protein L23a (peptide 2-3), one from TGF-beta induced gene (peptide 3-1) and one human TB2 gene (peptide 3-2). Of these examples, only peptides were loaded into a single kind of APC, RMA/HHD/B7.1, and no examples of a gene- loaded APC are shown. The attorney arguments on the bottom of p. 11 of the Response rely on common knowledge for asserting art-recognized genetic engineering techniques to express peptides from APCs without any indicia of authority for this statement. Pursuant to MPEP 2144.03, "ordinarily there must be some form of evidence in the record to support an assertion of common knowledge."

Furthermore, the Declaration under 37 CFR 1.132 filed 9/18/08 is insufficient to overcome the rejection of claims 15, 21-23, 30 and 43-45 based upon the enablement rejection under 35 U.S.C. 112, 1st paragraph, as set forth in the last Office Action of 3/18/08 because: the Declaration fails to set forth the facts and the showing is not

commensurate in scope with the claims for a peptide-loaded APC where the expressed or presented peptide bears all the properties as claimed.

The Declaration does not reference: the outstanding Office Action, the rejected claims and how the rejection is applied to the claims. The Declaration lists two references enclosed as Tirosh et al. Brit. J. Can. 97:1655-1663 (2007) and Eisenbach, Report to Ministry of Health "The effect of SNPs in Tumor Associated Antigens on the Immunogenicity of Peptide Based Vaccines" (pp. 1-8 (8/2007)) withour explaining the references or interpreting their relevance to the rejected claims. The Declarant does not explain how the references further support or enable the scope of the rejected claims.

The rejection is maintained because neither Applicants' attorney nor the Declarant has even taken the time to explain with sufficient clarity the relevance of the enclosed references to the instant rejected claims."

Applicants allegations on p. 10 of the Response of 6/17/09 summarize the 1.132 Declaration of Dr. Eisenbach and each of which have been carefully considered and are not found persuasive. The examiner has ascertained that the Declarant comments on pp. 2-4 of the Declaration seemingly correspond to the outstanding rejection. Here the Declarant alleges Lesterhuis et al. (Crit. Rev. Oncol./Hematol. 66:118-134 (2008)) reviews the state of the art for RNA transfected/loaded APCs and is cited for incorporating an article describing DC loaded with CEA peptides in CEA-expressing malignancies; and Example 1 of the specification and the Tirosh reference (cited in the PTO 892 form of 12/17/08) establish that methods are well known for loading APCs.

Response to Arguments

The examiner respectfully appreciates the analysis but is hard put to understand how this addresses the original grounds for rejection, namely, that Applicants have not yet substantiated with a reasonable number of working examples that the human colon carcinoma-derived TAA peptide(s) disclosed in the specification in fact could be presented by any APC in order to accomplish the required elicitation of a CTL response whether observed in vitro much less in vivo (i.e., the demonstration of an intended use). The claimed genus of peptides and APCs is not reasonably correlated with the

enablement provided in the specification or Tirosh for inducing a CTL response in vitro much less in vivo. As stated in the Office Action of 7/10/07:

> "The specification discloses general classes of MHC-class I binding, CTL-inducing peptides in Table 1. The inventive peptides shown to have MCH Class-I binding and CTL-inducing activity in vitro are those of SEQ ID NO: 6-27 (table 3), and the peptides shown to have putative MHC-Class I binding are of SEQ ID NO:29-55. None of the peptides are disclosed as being modified to contain a non-natural amino acid such as a peptide modification, a semi peptide modification, a cyclic peptide modification, a N-terminus modification, a C-terminus modification, a peptide bond modification, a backbone modification and a residue modification. The specification teaches peptide conjugates to other molecules or compounds (pp. 29 and 35). Thus the specification is not enabling for the breadth of the peptides encompassed by the instant claims. One skilled in the art would be left to identify not only the infinite polynuleotides expressed by the human colon carcinoma and to clone those nucleotides in order to identify proteins, but would then be required to identify the peptide epitopes that meet all of the limitations of the claims. One skilled in the art could not determine which of the infinite combination of modifications could be made to any class much less individual peptide based on the specification alone, because the specification does not define the specific positions and regions of the peptides which can be predictably modified and which regions are critical and the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful."

In response to applicant's argument that the applicant's invention is fully enabled for the genus of peptides being presented by the genus of APCs and inducing a CTL effect or response, it is noted that the features upon which applicant relies (i.e., peptides in Table 3 (p. 49); peptides in Table 5 (pp. 66-67); peptides having MHC binding activity in vitro (Figures 12A-12L); peptides having CTL inducing ability in vivo in animal model (Figures 13A, 13B, 14A, 14B, 15A and 15B); and peptides having CTL inducing ability in vivo in CaP patients (Figures 16A-D, 17A-C and 18A-E) *are not* recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from

the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). The rejection is maintained.

Enablement (2)

11. The rejection of Claims 1, 3-6, 9, 12-17, 21-23, 30, 36-39, 43-45 and 62 under 35 U.S.C. 112, first paragraph, is maintained because the specification is lacking in enablement for any peptide isolated from any protein expressed by any polynucleotide from any human colon carcinoma cell where the peptide has the ability to bind MHC Class I *and* elicit a peptide-specific CTL response and where the peptide optionally includes at least one non-natural modification.

For purposes of review the rejection was maintained in the Office Action of 3/18/08 as follows:

A) On pp. 11-13 of the Response of 1/10/08 Applicants allege the claims are fully enabled for the breadth of peptides because: 26 examples of peptides from colorectal genes are shown in Table 2, three peptides derived from 1-8D interferon induced transmembrane protein 2 (SEQ ID NO:59) are shown to be antigenic and immunogenic in HHD mouse model and the working models in the specification provide "sufficient guidance for one of skill in the art to determine other TAA peptides of a protein encoded by a polynucleotide overexpressed in human colon carcinoma cells without undue experimentation. Applicants then assert that the literature provided as extrinsic support show peptides similarly identified without undue experimentation.

The examiner submits that Applicants specification as originally filed does not support the breadth of TAA peptides meeting all of the limitations of the instant claims. The overexpressed proteins from colon carcinoma were screened for putative HLA-A2.1 restricted peptides using the "independent binding of individual peptide side-chains" software (Parker et al., 1994). HLA-A2.1-restricted peptides from the selected genes were selected according to its consensus binding motifs are shown in Table 2. Of the 26 peptides, 7 were shown to be immunogenic in vivo and 3 peptides were from human 1-8D interferon induced transmembrane protein 2 (SEQ ID NO:59). Not all of the putative peptides in Table 2 were antigenic under assay conditions, only 7 were immunogenic, and 3 of the 7 are all from the same protein (human 1-8D interferon induced transmembrane protein 2). Applicants own data in the specification are dispositive to the assertion that just any peptide can be designed and that would predictably bind MHC to promote a CTL response in vitro much less in vivo.

The reference copies provided with the Response are acknowledged but Applicants have not provided any explanation as to how the references are relevant to the instant claimed peptides derived from human colon carcinoma TAA. For example, are any of the reference TAA-derived peptides also described in the specification as overexpressed, colon cancer-derived TAAs?

Machlenkin describes peptides from PAP-3 ((Can. Res. 65:6435-6442 (2005) and (Can. Immunol. Immunother.56:217-226 (2007)) in prostate cancer and peptides from STEAP from prostate cancer (Can. Res. 65:6435-6442 (2005)). Applicants' claims specifically exclude STEAP-derived peptides so the reference is irrelevant. Applicants' specification teaches "The oldest discovered **prostate-restricted antigens** have included prostate-specific antigen (PSA), prostate-specific membrane antigen (PSMA) and prostatic acid phosphatase (PAP)" [0140]. How is PAP-3 related to a human colon carcinoma TAA and what is the relevancy of the reference?

Bar-Haim (Br. J. Can. 91:398-407 (2004) describes peptides from MAGE-A8 protein in bladder cancer. Applicants' specification does not define much less mention MAGE-A8 being a colon cancer TAA. Bar-Haim describes MAGE-A8 protein expression occurring in 44% of colorectal carcinomas but not in any normal colon samples (p. 398, Col. 2, ¶3). Thus MAGE-A8 protein does not even meet the requirements of the claims, which is that the protein is overexpressed, implying that some basal level of expression would need to occur in a normal cell. What is the relevancy of the reference?

Carmon (Int. J. Can. 85:391-397 (2000)) describes peptides from MUC1 protein in breast cancer. Applicants' specification does not define much less mention MUC1 being an overexpressed colon cancer TAA. What is the relevancy of the reference?

Carmon (J. Clin. Invest. 110:453-462 (2002) describes peptides from BA46 protein in breast cancer. Applicants' specification does not define much less mention MUC1 being an overexpressed colon cancer TAA. What is the relevancy of the reference?

Stepensky (Clin. Exp. Immunol. 143:139-149 (2005) describes peptides from MUC-1 in lung carcinoma. Applicants' specification does not define much less mention MUC1 being an overexpressed colon cancer TAA. What is the relevancy of the reference?

Applicants have not cited any references that are enabling for the scope of peptides encompassed by the claims at the time of application filing. Applicants have demonstrated that only a small percentage of colon carcinoma TAA-derived peptides modeled from the software program were immunogenic thus one of skill in the art could not reliably and predictably use peptides designed from the software and consensus binding motifs without further experimentation to determine which peptides could bind MHC and elicit a CTL response. The claims further encompass modified peptides, thus the claim scope far exceeds what Applicants have actually demonstrated by working example in the specification or what was known in the art for colon carcinoma-derived immunogenic peptide at the time of filing.

B) On p. 13 of the Response of 1/10/08 Applicants have urged the Office to consider "post-filing experimental results obtained in the laboratory of the present inventors to show that some amino acid modifications of 1-8D peptide 3-7 and all modifications of 1-8D peptide 3-5 induced a CTL response."

The examiner respectfully submits that the data has not been considered because of the improper presentation under MPEP 2162.05 and 37 CFR 1.132:

> "§ 1.132 Affidavits or declarations traversing rejections or objections. When any claim of an application or a patent under reexamination is rejected or objected to, any evidence submitted to traverse the rejection or objection on a basis not otherwise provided for must be by way of an oath or declaration under this section. [48 FR 2713, Jan. 20, 1983, effective Feb. 27, 1983; revised, 61 FR 42790, Aug. 19, 1996, effective Sept. 23, 1996; revised, 65 FR 54604, Sept. 8, 2000, effective Sept. 8, 2000; revised 65 FR 57024, Sept. 20, 2000, effective Nov. 29, 2000]."

Applicants are invited to resubmit the new data in the form of 1.132 Declaration signed by one of the named inventors and to identify literal support in the original specification for the examples of the modified peptides in order to avoid raising any issues of new matter. Alternatively, Applicants are invited to file a C-I-P application containing the new data.

C) On pp. 13-14 of the Response, Applicants allege that because the specification describes numerous prophetic or hypothetical examples of non-natural modifications to peptides using positions P1-P9 as guidance, that one of skill in the art could design and model TAA peptides of 8 to 10 amino acid residues from any colon-cancer associated TAA.

The examiner submits that the 7 operative peptides meeting the claim limitations filed in the original specification were not modified from the corresponding stretch of amino acid residues in the corresponding colon cancer protein. All of them corresponded to the native sequence structure from the native protein. Applicants' new data allegedly describes examples of modified peptides for the immunogenic peptides 3-5 and 3-7 from 1-8D interferon inducible protein 2, however, that information has not been considered for the reasons set forth above. Applicants are invited to file the data under a 1.132 Declaration to advance the examination proceeding.

Finally, Applicants specification in Table 2 teaches several non-operative embodiments for peptides which were designed to correspond to native protein structures, and Applicants are now urging the Office to believe that one could further modify a peptide of unpredictable immunogenicity to create an immunogenic, modified peptide absent a proper showing of expected results."

The rejection was maintained in the Office Action of 12/17/08 as follows:

"Applicants' allegations on pp. 12-14 of the Response of 9/18/08 and the 1.132 Declaration have been considered and are not found persuasive. Applicants allege that because they have isolated a total of seven immunogenic peptides, that producing and screening immunogenic peptides from any TAA protein expressed by any colon carcinoma is predictable and within ordinary skill; and the "Summary" report discloses 4 variants of peptide 3-7 and 8 variants of peptide 3-5 and which are shown to bind HLA-A2.1 except for the I/A substitution for peptide 3-5.

Response to Arguments

While the specification may enable general methods for selecting and screening a peptide, this does not necessarily place applicant in possession of any overexpressed parent protein from a human colon cancer, an immunogenic peptide from that protein, or a polynucleotide encoding the peptide. The Tirosh reference discloses the same data presented in Example 1 of the specification without expanding on the number or kind of peptides meeting the claim requirements.

The Summary data has been considered but appears to represent new matter. The original specification does not contemplate these peptide variants of SNPs for the human 1-8D interferon inducible protein 2, and even assuming *arguendo*, they were contemplated it is not predictable that they would function in the manner demonstrated in the Summary report. Additionally, these peptide examples are not further enabling for the infinite genus of peptide classes encompassed by the claims. The Summary Report has not been entered on the PTO 892 form and has been placed in the file. Applicants are requested to identify in the original specification and/or priority document where written description support for the SNP of the human 1-8D interferon inducible protein 2 protein and peptide variants of the SNP is found.

The Declaration under 1.132 is insufficient in overcoming the rejection for the same reasons set forth under section 6 above."

Applicants' allegations on p. 10 of the Response of 6/17/09 summarize the 1.132 Declaration of Dr. Eisenbach and each of which have been carefully considered and are not found persuasive. The examiner has ascertained that the Declarant comments on pp. 4 -6 of the Declaration seemingly correspond to the outstanding rejection. Here the Declarant alleges: the TAA protein must be overexpressed by human colon carcinoma cells, and the genes that are overexpressed by human colon carcinoma cells are known and available in the literature. They were known at the time the present invention was made. Applicants relied on Zhang et al. (Science 276:1268-1272 (1997); cited in the IDS of 9/23/05) for predictive peptides and reduced to practice 500 peptides and tested with respect to HLA-A2 haplotype antigen-presenting cells and a mouse model having the human HLA-A2 gene. The ordinary artisan would simply start from the 26 overexpressed genes and model them against the APC haplotype in question to find the putative peptides that are most likely to fit into the pocket of that APC and then repeat

the tests using mice that are transgenic for that particular human haplotype of interest and using the APCs of that haplotype.

Response to Arguments

The examiner respectfully submits that the Declarant has identified 26 over-expressed polynucleotides and the corresponding protein products in the human colon carcinoma cell line, HCT-15, yet they urge the Office to believe that these 26 overexpressed products represent the entire over-expression profile for the universe of human colon carcinomas without citing authority for this proposition (MPEP 2144.03, "ordinarily there must be some form of evidence in the record to support an assertion of common knowledge.").

Secondly, in response to applicant's argument that the invention is fully enabled for the genus of peptides obtained from any over-expressed human colon carcinoma including comprising non-natural modifications and further capable of inducing a CTL effect or response, it is noted that the features upon which applicant relies (i.e., peptides in Table 3 (p. 49); peptides in Table 5 (pp. 66-67); peptides having MHC binding activity in vitro (Figures 12A-12L); peptides having CTL inducing ability in vivo in animal model (Figures 13A, 13B, 14A, 14B, 15A and 15B); and peptides having CTL inducing ability in vivo in CaP patients (Figures 16A-D, 17A-C and 18A-E) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). The rejection is maintained.

Thirdly, Applicants have not demonstrated (and do not claim) a structure/ function correlation for the genus of TAA peptides of 8-10 residues corresponding to the any protein from any over-expressed polynucleotide in any human colon carcinoma much less where any one of the peptides has been non-naturally modified, and where the genus of these peptides "promote effective binding to a MHC Class I molecule to elicit a CL response." For example, if Applicants were to amend the claims to recite the relevant identifying characteristics, e.g., 1) a complete structure, ii) partial structure, iii) physical and/or chemical properties, or iv) functional characteristics coupled with correlation between structure and function for the genus of TAA peptides, then the skilled artisan would be reasonably enabled to practice using the instant claimed products. The rejection is maintained.

Enablement (3)

12. The rejection of Claims 5, 6 and 59 (and now Claims 30- 45) under 35 U.S.C. 112, first paragraph, is maintained in lacking enablement for any immunogenic peptide derived from the protein encoded by the nucleotide of SEQ ID NO:58 (human 1-8D interferon inducible protein 2) or encoded by the nucleotide of SEQ ID NO: 60 (human 1-8D interferon inducible protein 2 polymorphism).

For purposes of review, the rejection was maintained for the following reasons:

"Applicants' allegations on pp. 14-17 of the Response of 1/10/08 have been considered but are not found persuasive. Applicants allege there is very little difference between the nucleotide sequence of SEQ ID NO: 59 for human 1-8D interferon inducible protein 2 and the nucleotide sequence of SEQ ID NO:60 or the encoded protein thereof (SEQ ID NO: 61) for the polymorphic human 1-8D interferon inducible protein 2 so that the 3 peptides shown in the specification to bind MHC and elicit CTLs (from the protein encoded by SEQ ID NO: 59) would be the same as the peptides from the protein of SEQ ID NO:61 at inducing the response. Further, because the peptide domains for the 3 peptides fall outside of the polymorphic residue(s) of SEQ ID NO:60 and 61, the same 3 immunogenic peptides

would occur in the structure of the protein of SEQ ID NO:61 as the protein encoded by the nucleotide of SEQ ID NO:58.

The examiner respectfully submits that the claim scope is not limited to any of the 3 peptides shown in the specification but to any peptide falling within the structure of the protein encoded by the nucleotide of SEQ ID NO:58 (human 1-8D interferon inducible protein 2) or encoded by the nucleotide of SEQ ID NO: 60 (human 1-8D interferon inducible protein 2 polymorphism). The proteins are considered to be separate and distinct because they have different sequence structures."

The rejection was maintained in the Office Action of 12/17/08 as follows:

"Applicants' allegations on pp. 14-15 of the Response of 9/18/08 have been considered and are not found persuasive. Applicants reiterate the allegation that just because immunogenic peptides from human 1-8D interferon inducible protein 2 were obtained by following the protocol in the specification, that the ordinary artisan could practice making any other immunogenic peptides without undue experimentation.

Response to Arguments

Applicants' specification and the Tirosh reference do not teach the amount of experimentation required for obtaining peptides from human 1-8D interferon inducible protein 2 and screened for immunogenicity before the 3 functional peptides were identified. What was the total number of peptides from human 1-8D interferon inducible protein 2 required to be generated before the first 3 were identified? Still further, Applicants have ignored the predictability prong of the Wands analysis. The examiner cited several references in the Office Action of 7/10/07 which discussed the unpredictability of selecting CTL immunogenic peptides. Applicants have established they are enabled for 3 peptides obtained from human 1-8D interferon inducible protein 2. Applicants have not established that an immunogenic peptide could be obtained from the SNP for human 1-8D interferon inducible protein 2 encoded by the polynucleotide of SEQ ID NO:61.

The rejection is maintained because Applicants have yet to provide data to support the full scope of peptides encompassed by the claims.

Applicants allegations on p. 10 of the Response of 6/17/09 summarize the 1.132 Declaration of Dr. Eisenbach and each of which have been carefully considered and are not found persuasive. The examiner has ascertained that the Declarant comments on pp. 6-10 of the Declaration seemingly correspond to the outstanding rejection. Here the Declarant alleges: it is a lot of work to screen the approximately 500 peptides from the 26 colorectal-associated genes indicated in Table 2 of the present specification and in Table 1 of Tirosh et al. (2007), but still, 500 is a relatively small finite number that can be screened without undue experimentation…and, "No inventive steps are necessary to complete such a screen"…and, "The amount of time depends on how many people are working on it and how many animals are being used simultaneously. It took my laboratory one year to do this but it could have been done faster with more people and

more funding. The work was certainly not "undue," but rather involved standard routine experimental work."

Response to Arguments

The examiner respectfully submits that as much as Declarant has established that the methods involve routine experimentation at the time of filing (but are otherwise time consuming and costly), Declarant has addressed only one prong of the Wands analysis; Declarant has omitted how the ordinary artisan could reasonably predict a structure/function correlation for the genus of peptides having all of the instant claimed structural properties:

a) TAA peptide of eight to ten amino acid residues from a protein encoded by a polylpeptide overexpressed in any human colon carcinoma cell

b) the TAA peptide includes optionally at least one non-natural modification

c) the second residue from the N-terminus of the TAA peptide and the C-terminal residue of the TAA peptide are (i) hydrophobic or hydrophilic or (2) neutral, hydrophobic or aliphatic natural amino acid residues

d) the second residue from the N-terminus of the TAA peptide and the C-terminal residue of the TAA peptide are (i) hydrophobic or hydrophilic or (2) neutral, hydrophobic or aliphatic natural amino acid residues, and/or

e) the at least one non-natural modification is selected from the group consisting of a peptide modification, a semi peptide modification, a cyclic peptide modification, a N-terminus modification, a C-terminus modification, a peptide bond modification, a backbone modification, and a residue modification,

and also having the ability to bind MHC Class I molecule and elicit a CTL response (irrespective of whether the CTL response is in vitro or in vivo)

The rejection is maintained.

Written Description

13. The rejection of Claims 1, 3-6, 9, 12-17, 21-23, 30, 36-39, 43-45 and 62 under 35 U.S.C. 112, first paragraph, is maintained as failing to comply with the written description requirement because Claims 1, 3-7, 9, 12-17, 21-23, and 62 (and new Claims 63 and 64) recite the negative proviso, "*is not a six transmembrane epithelial antigen of the prostate (STEAP) protein*" in Claim 1, which does not find original support in the specification.

For purposes of review, the rejection was set forth in the Office Action of 3/18/08 as follows:

"The use of a negative limitation is used to define the invention in terms of what it is not, rather than distinctly and particularly claiming a specific peptide or class of peptides that meet the claim requirements and that is supported (and enabled) in the specification. Under MPEP 2173.05(i) "Any negative limitation or exclusionary proviso must have basis in the original disclosure."

The specification defines several putative antigenic peptides derived from proteins associated with human colon carcinoma in Table 2, antigenic peptides in Table 3 and immunogenic peptides (underlined peptides) in Table 3, but does not provide specific written support for the negative limitation "*is not a six transmembrane epithelial antigen of the prostate (STEAP) protein.*" Applicants have not and cannot identify per se support in the specification for the negative limitation as presently recited. Applicants are requested to identify the exact page, paragraph and line where the negative proviso is taught in the specification (MPEP 2173.05(i)). Further, by excluding the peptide(s) of the STEAP class of proteins, the claims encompass myriad other peptides that are not fully supported or enabled by the record evidence. One skilled in the art would conclude that Applicants were not in possession of the invention for any isolated TAA peptide of 8-10 amino acid residues which promotes binding to MHC class, elicits a CTL response, is obtained from a protein overexpressed in human colon cancer, and "*is not a six transmembrane epithelial antigen of the prostate (STEAP) protein*" when instead the only other species of peptides, distinctly and particularly described in the specification are the peptides in Tables 2 and 3."

The rejection was maintained in the Office Action of 12/17/08 as follows:

"Applicants' allegations on pp. 15-18 of the Response of 9/19/08 have been considered and are not found persuasive. Applicants excerpt the MPEP under sections 2173.01 and 2173.05(i) and part of the decision from *In re Johnson* 194 USPQ 196 (CCPA 1977) to assert "the positive recitation in the present specification of STEAP indeed

provides adequate written description to excise what applicants are not entitled to from their claimed invention by the use of negative limitations."

Response to Arguments

Some earlier cases before *Johnson* were critical of negative limitations because they tended to define the invention in terms of what it was not, rather than pointing out the invention. Thus In re Schechter, 205 F.2d 185, 98 USPQ 144 (CCPA 1953), the court observed that the limitation "R is an alkenyl radical other than 2-butenyl and 2,4-pentadienyl" was a negative limitation that rendered the claim indefinite because it was an attempt to claim the invention by excluding what the inventors did not invent rather than distinctly and particularly pointing out what they did invent.

The examiner submits that Applicants wish to obtain patent coverage for any peptide of 8-10 amino acid residues in length from any known or yet to be discovered TAA protein expressed by any human colon carcinoma cells. It is clear from the specification and the Tirosh reference that from over 500 putative TAA peptides derived from 26 overexpressed genes in colon carcinoma, that only seven (7) peptides were antigenic and immunogenic in HHD mice. Of these 7, three were from "human 1-8D gene from interferon inducible gene" (peptides 1-6, 3-5 and 3-7), one from actin binding protein (peptide 1-11), one from human ribosomal protein L23a (peptide 2-3), one from TGF-beta induced gene (peptide 3-1) and one human TB2 gene (peptide 3-2). Applicants' claims recite a broader genus of protein families than supported by the original disclosure even with the negative proviso.

Thus it is more than apparent that the universe of colon-cancer derived TAA proteins is not supported by the specification much less that any of the 26 proteins examined would necessarily even yield a peptide meeting all of the required limitations of the claims. Without this specific information, it is impossible to identify the claimed subject matter. Applicants' claims do not exclude these unknown proteins or their corresponding peptides and it is impossible to grant patents rights without a full disclosure of the metes and bounds of the claimed invention. For example, how would another inventor know if one were infringing this claimed invention if the precise epitopes were not disclosed?"

Applicants' allegations on pp. 10-14 of the Response of 6/17/09 have been considered and are not found persuasive.

a) Applicants allege MPEP 2173.05(i) teaches "The current view of the courts is that there is nothing inherently ambiguous or uncertain about a negative limitation."

Response to Arguments

The examiner respectfully submits that the excerpted text in the Response excludes the immediately following sentence, namely, that there is nothing inherently ambiguous or uncertain about a negative limitation "*So long as the boundaries of the patent protection are set forth definitely, albeit negatively...*" (MPEP 2173.05(i)). Here and again, Applicants have not defined the genus of TAA peptides from 8-10 residues in size obtained from any protein of any over-expressed polynucleotide in any human colon carcinoma by sufficient *structural characteristics* so as to confer whether those

same peptides possess the *functional characteristics* of binding MHC Class I molecule ***and*** eliciting a CTL response (irrespective of whether the CTL response is in vitro or in vivo). Applicants attention is drawn to the Written Description Guidelines (66 FR 1099 (Jan. 5, 2001); 1242 O.G. 168 (Jan. 30, 2001) revised training materials 3/25/08) where disclosure of the specification, drawings or structural chemical formulas and relevant identifying characteristics (e.g., (1) a complete structure, ii) partial structure, iii) physical and/or chemical properties, and/or iv) functional characteristics coupled with correlation between structure and function) are evaluated in the determination of possession for the genus of peptides at the time of filing. Accordingly and herein reiterated, Applicants have not claimed nor defined the boundaries of the instant peptides to permit claiming the genus of peptides by negative proviso. Applicants have not demonstrated that they were possession of those peptides at the time of filing.

b) Applicants allege they have specifically identified 26 genes that are overexpressed in human colon carcinoma cells from which to screen TAA peptides; the experiments in Example 1 of the specification demonstrate the structure/function relationship between haplotype (MHC class I) HLA-A2.1 and peptides that can fit into the pocket of the HLA-A2.1 haplotype; and the present specification, including Example 1 and Table 1, teaches how to correlate structure and function between different haplotypes and different TAA peptides and there are computer models based on the structure/function correlations for some haplotypes.

Response to Arguments

Applicants have not demonstrated a reasonable number of working examples of peptides predicted from the structure/function computer modeling for the genus of peptides having all of the instant claimed structural properties:

a) TAA peptide of eight to ten amino acid residues from a protein encoded by a polylpeptide overexpressed in any human colon carcinoma cell

b) the TAA peptide includes optionally at least one non-natural modification

c) the second residue from the N-terminus of the TAA peptide and the C-terminal residue of the TAA peptide are (i) hydrophobic or hydrophilic or (2) neutral, hydrophobic or aliphatic natural amino acid residues

d) the second residue from the N-terminus of the TAA peptide and the C-terminal residue of the TAA peptide are (i) hydrophobic or hydrophilic or (2) neutral, hydrophobic or aliphatic natural amino acid residues, and /or

e) the at least one non-natural modification is selected from the group consisting of a peptide modification, a semi peptide modification, a cyclic peptide modification, a N-terminus modification, a C-terminus modification, a peptide bond modification, a backbone modification, and a residue modification,

and also having the ability to bind MHC Class I molecule and elicit a CTL response (irrespective of whether the CTL response is in vitro or in vivo)

The rejection is maintained.

New Grounds for Rejection

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

14. Claims 1, 12, 13, 14, 15, 16, 21, 22, and 23 are rejected under 35 U.S.C. 102(a) as being anticipated by Tsang et al. (Can. Res. 61:7568-7576 (10/15/01)).

Claims 1 and 12-14 are interpreted as being drawn to a TAA peptide of 8-10 residues in length from a protein encoded by a polynucleotide over-expressed in a human colon carcinoma that *may* include one non-natural modification to the peptide and binds to an MHC Class I molecule to elicit a CTL response (Claim 1), where the MHC Class I molecule is HLA.A2.1 (Claim 12), the peptide includes at least one non-natural modification (Claim 13), the at least one non-natural modification is a peptide modification or a residue modification (Claim 14).

Claims 15, 16 and 21-23 are interpreted as being drawn to a composition comprising the peptide of Claim 1 and pharmaceutical carriers (Claim 15), which includes a helper peptide (Claim 16) or the composition is a cell composition comprising an APC with the peptide (Claim 21), and the APC is a DC cell (Claim 22), and the APC is loaded with the peptide (element c of Claim 23).

Tsang teaches using a 9-mer CTL epitope, CAP-6D, of TAA CEA which is expressed on human colon carcinoma and comprising a single amino acid change compared to the native CAP-1 epitope (which is considered non-naturally occurring). Tsang showed CEA-specific T cells are more effectively activated using as APCs, peptide-pulsed DCs further infected with a vector comprising B7-1 (considered a helper peptide), as compared with peptide pulsed DCs infected with wild-type vector or uninfected peptide-pulsed DCs. The specificity of the CTLs was tested for lysis of human colon carcinoma cell lines (HLA.A1,2) (se Table 3).

15. Claims 1, 3, 12, 13, 14, 15, 21, 22, 23 and 62 are rejected under 35 U.S.C. 102(a) as being anticipated by Trojan et al. (Lung Can. 36(2):151-158 (May 2002)).

The interpretation of Claims 1, 12, 13, 14, 15, 21, 22, and 23 is discussed above under section 14. Claim 13 is interpreted as the peptide having at the 2nd residue from the N-terminus and the C-terminus, a hydrophobic or hydrophilic residue, or a neutral, hydrophobic or aliphatic residue. Claim 22 is interpreted as being drawn to a composition comprising the peptide of Claim 1 and pharmaceutical carriers, where the composition further comprises a B cell as the APC. Claim 62 is interpreted as being drawn to a peptide of Claim 1 and does not include at least one non-natural modification.

Trojan show that antigen specific CTL specific for an immunogenic peptide ILYENNVIT (184-192) of Ep-CAM and a heteroclitic modified variant peptide

(ILYENNVIV; Ep-2H), exist in HLA-A2 patients with Ep-CAM-expressing colorectal cancers and can be expanded from PBMCs in vitro (Table 1) and where autologous PBMCs were used as APCs pulsed with peptide (section 2.6 and 2.7 in Methods and Materials).

16. Claims 1, 12, 13, 14, 15, 16, 21, 22, and 23 are rejected under 35 U.S.C. 102(b) as being anticipated by Abrams et al. (Cell. Immunol. 182:137-1515 (1997)).

The interpretation of Claims 1, 12, 13, 14, 15, 16, 21, 22, and 23 is discussed above under section 14. Claim 22 is interpreted as being drawn to a composition comprising the peptide of Claim 1 and pharmaceutical carriers, where the composition further comprises a B cell as the APC.

Abrams teaches generating human HLA-A2-restricted, CD8+ CTL epitopes reflecting 2 distinct K-*ras* proto-oncogene codon 12 mutations, which are 10-mer sequences spanning ras sequence 5-17 and having amino acid substitution of Gly for Asp, Cys or Val at position 12. HLA-restricted peptide-specific CD8+ T cells are generated using culture conditions containing autologous APC, the mutant ras peptide as antigen and low dose IL-2, where the IL-2 is considered a helper peptide. The Ag-specific, MHC Class I restricted CD8+ CTL line was generated in vitro from post-vaccination lymphocytes of a colon carcinoma patient whose primary tumor also contained a K-*ras* Asp 12 mutation. Thus the mutation to K-ras from the colon caner patient is non-natural occurrence compared to the wild-type or natural K-ras protein. Abrams teaches that PBMC served as APC with peptide for pre-incubation conditions

but were later replaced with autologous EBV-B cells as APC (p. 139, bottom Col. 2 to p. 140, top of Col. 1).

Conclusion

17. Claim 59 is drawn to the human 1-8D interferon inducible protein 2 polymorphism of SEQ ID NO: 61 and is free from prior art.

18. Claims 7, 63 and 64 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. Claims 7, 63 and 64 are drawn to peptide 3-7 (peptide of SEQ ID NO: 27 from 1-8D interferon inducible gene protein), peptide 1-6 (peptide of SEQ ID NO: 11 from 1-8D interferon inducible gene protein), and peptide 3-5 (peptide of SEQ ID NO: 25 from 1-8D interferon inducible gene protein), respectively. These peptides have been tested in vitro and in vivo experiments with results shown in Figures 4-10.

19. The following post-filing date references are considered relevant but are not relied upon as art:

Andreu et al. (Can. Res. 66(4):1949-1955 (Feb 2006)) showing over-expression of IFITM2 (human 1-8D interferon inducible protein 2) in human colon cancer; and

Nakamura et al. (US 20060204960; filed 9/19/03) and Nakamura et al. (US 20050259483; filed11/24/05) teaching making antigenic peptides for CTLs from numerous expressed proteins such as IFITM2 from cancers including colon cancer but have not reduced any examples to practice.

20. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lynn Bristol whose telephone number is 571-272-6883. The examiner can normally be reached on 8:00-4:00, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Lynn A. Bristol/
Examiner, Art Unit 1643
Temporary Full Signatory Authority